REMARKS

Reconsideration of the present application is respectfully requested in view of the above amendments and the following remarks. Claims 1-45 are pending in the application; claims 1-11, 13-19, 27-37, and 39-45 are currently under examination, and claims 12, 20-26, and 38 are withdrawn. Without acquiescence to any rejection, or prejudice to pursuing the encompassed subject matter in a related divisional, continuation, continuation-in-part, or reissue application, claims 1, 13, and 39 are amended to particularly point out and distinctly claim certain embodiments of Applicants' invention. No new matter has been added by the amendments. Support for the amendments can be found in the claims and in the specification as originally filed, for example, at page 18, lines 7-9.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, INDEFINITENESS

A. The Examiner rejected claims 1-11, 13-19, 27-37, and 39-45 under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. The Examiner asserts that the recitation "one" is indefinite, asserting that the entity denoted by "one" is unknown.

Applicants traverse this rejection and submit that the instant claims are clear. In particular, Applicants submit that persons skilled in the art would understand that the recitation "one another" refers to each of the recited claim features. Nonetheless, without acquiescence, the recitation "one" has been deleted from claim 1, thereby obviating this rejection.

Applicants, thus, submit that the instant claims satisfy the requirements of definiteness under 35 U.S.C. § 112, second paragraph, and respectfully request withdrawal of this rejection.

B. The Examiner rejected claims 13 and 39 under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. The Examiner asserts that the recitation "a reactive aldehyde group" lacks proper antecedent basis in base claims 12 and 38.

Applicants traverse this rejection and submit that the instant claims are clear. Nonetheless, without acquiescence, claims 13 and 39 as amended herewith recite, in pertinent part, the protein conjugate according to claim 11 (or claim 37), wherein the reactive group of the

non-peptide polymer is a reactive aldehyde group at both ends thereof. It is respectfully submitted that base claims 11 and 37 provide proper antecedent basis for the recitation "the reactive group of the non-peptide polymer," and for the recitation "a reactive aldehyde group," thereby obviating this rejection.

Accordingly, Applicants submit that the instant claims satisfy the requirements of definiteness under 35 U.S.C. § 112, second paragraph, and respectfully request withdrawal of this rejection.

REJECTIONS UNDER 35 U.S.C. § 102

A. The Examiner rejected claims 1, 4-10, 14-18, 27, 30-36, and 40-44 under 35 U.S.C. § 102(b) for alleged lack of novelty over Pettit (U.S. Patent No. 6,441,136). The Examiner asserts that Pettit teaches a protein conjugate comprising a physiologically active polypeptide that is covalently linked by fusion to an Fc region, and a non-peptide polymer, such as PEG. The Examiner then asserts that this composition anticipates the instant claims.

Applicants traverse this rejection and submit that the instant claims satisfy the requirements of novelty over Pettit. Embodiments of the instant claims relate, in pertinent part, to protein conjugates comprising a physiologically active polypeptide, a non-peptide polymer, and an immunoglobulin Fc fragment, wherein the peptide and the immunoglobulin Fc fragment are covalently linked through the *non*-peptide polymer.

Pettit fails to disclose each feature of the instant claims. For example, as recognized by the Examiner in not rejecting the related subject matter of claims 2-3 over Pettit, this reference fails to disclose a polypeptide that is covalently linked to an immunoglobulin Fc fragment through a *non*-peptide polymer. Instead, Pettit are limited to fusion proteins of peptides and Fc fragments, which are necessarily linked through a peptide linkage (*see, e.g.,* Example 2 of Pettit). Indeed, nowhere does Pettit teach or even remotely suggest the use of a *non*-peptide polymer to covalently link a physiologically active peptide to an immunoglobulin Fc fragment, as presently claimed. Therefore, it is respectfully submitted that Pettit fails to anticipate the instant claims.

In view of the deficiencies of Pettit, Applicants submit that the instant claims satisfy the requirements of novelty over this reference, and respectfully request withdrawal of this rejection under 35 U.S.C. § 102(b).

B. The Examiner rejected claims 1-11, 13-19, 27-37, and 39-45 under 35 U.S.C. § 102(e) for alleged lack of novelty over DeFrees *et al.* (U.S. Patent No. 7,125,843). The Examiner asserts that DeFrees *et al.* teach a conjugate molecule comprising an antibody that is covalently linked to a biologically active polypeptide, such as erythropoietin. The Examiner then asserts that the antibody of DeFrees *et al.* inherently contains an immunoglobulin Fc fragment, and, thus, essentially asserts that the conjugated antibody of this reference falls within the scope of the presently claimed protein conjugates.

Applicants traverse this rejection and submit that the instant claims satisfy the requirements of novelty over DeFrees *et al.* As noted above, embodiments of the instant claims relate, in pertinent part, to protein conjugates comprising a physiologically active polypeptide, a non-peptide polymer, and an immunoglobulin Fc *fragment*, wherein the peptide and the immunoglobulin Fc fragment are covalently linked through the *non*-peptide polymer.

DeFrees *et al.* fail to disclose each feature of the instant claims. For instance, DeFrees *et al.* fail to disclose a protein conjugate comprising an Fc *fragment* that is linked to a polypeptide through a *non*-peptide polymer. In this regard, Applicants respectfully disagree with the Examiner's assertion that DeFrees *et al. inherently* disclose the use of an immunoglobulin Fc *fragment*, merely because they disclose a whole *antibody* (*see* the Action, page 5) as one possible component of a conjugate molecule. Instead, as disclosed in the specification, it is respectfully submitted that the antibody-based conjugates of DeFrees *et al.* do not fall within the scope of the instant claims, whether inherently or otherwise.

The immunoglobulin Fc *fragment* of the instant claims represents a structurally distinct molecule as compared to the whole antibody of DeFrees *et al.*, rendering the presently claimed conjugates novel over those of DeFrees *et al.* On this point, Applicants note that an "immunoglobulin Fc *fragment*" is expressly defined in the specification to *exclude* whole antibodies, such as the antibody of DeFrees *et al.* relied upon by the Examiner (*see, e.g.,* page 11,

lines 9-15 of the specification). Specifically, the specification states that an "immunoglobulin Fc fragment" does ***not*** contain "the variable regions of the heavy and light chains, the heavy-chain constant region 1 (CH1) and the light-chain constant region 1 (CL1) of the immunoglobulin." *Id.*

In contrast, persons skilled in the art would understand that the antibody of DeFrees *et al.* contains these structural features. Indeed, DeFrees *et al.* expressly define an "antibody" as "an immunoglobulin molecule which is able to *specifically bind to a specific epitope on an antigen*" (*see, e.g.,* column 36, lines 65-37 of DeFrees *et al.*)(emphasis added), in part, because DeFrees *et al.* rely on such functional and inherent structural characteristics in their use of an antibody as a *targeting agent* (*see, e.g.,* column 68, last full paragraph of DeFrees *et al.*). However, as noted above, the immunoglobulin Fc fragments of the instant claims do not contain the structural features required to *specifically bind to a specific epitope on an antigen* (*e.g.,* variable regions), as in DeFrees *et al.*, because the conjugates containing those Fc fragments are used as drug carriers, not targeting agents. With respect to their function as drug carriers, Applicants note that the instant immunoglobulin Fc fragments have a relatively low molecular weight as compared to whole immunoglobulin molecules, providing significant advantages in the preparation, purification, and yield of conjugates. Moreover, since the immunoglobulin Fc fragments of the instant claims do not contain Fab fragments, the compositions obtained therefrom not only have increased homogeneity, but are less antigenic (*see, e.g.,* page 12, lines 13-20 of WO 2005/047336). Therefore, by disclosing a structurally distinct molecule, it is respectfully submitted that DeFrees *et al.* fail to disclose, *inherently* or otherwise, a protein conjugate comprising a physiologically active polypeptide, a non-peptide polymer, and an immunoglobulin Fc fragment, as presently claimed.

While Applicants recognize that the Examiner must give the claims the broadest reasonable interpretation during prosecution, Applicants also respectfully submit that such an interpretation must be *consistent with the specification* and the understanding of a person skilled in the art. *See, e.g., In re Cortwright*, 165 F.3d 1353 (Fed. Cir. 1999). Here, since the specification expressly defines an "immunoglobulin Fc *fragment*" to *exclude* certain structural features that are inherent in a whole antibody, then it is axiomatic under a section 102 analysis

that the instant claims cannot be construed to read on the conjugates of DeFrees *et al.*, wherein those conjugates are limited to whole antibodies, or other "agents" that likewise fail to read on an immunoglobulin Fc *fragment*.

This deficiency of DeFrees *et al.* is especially acute given the further failure of this reference to disclose a protein conjugate comprising an immunoglobulin Fc *fragment* that is covalently linked to a physiologically active polypeptide through a *non*-peptide polymer. Indeed, with regard to Fc fragments, DeFrees *et al.* are limited to fusion proteins comprising Fc fragments (*e.g.,* Enbrel®), necessarily comprising peptide linkers, as opposed to conjugates of Fc fragments that utilize a *non*-peptide polymer as a linker, as presently claimed. Therefore, DeFrees *et al.* fail to anticipate the instant claims.

Given the failure of DeFrees *et al.* to disclose a conjugate molecule comprising an "immunoglobulin Fc *fragment*," as presently claimed, wherein that Fc fragment is covalently linked to a polypeptide through a *non*-peptide polymer, Applicants submit that the instant claims satisfy the requirements of novelty over this reference. Applicants, thus, respectfully request withdrawal of this rejection under 35 U.S.C. § 102(e).

OBVIOUSNESS-TYPE DOUBLE PATENTING

The Examiner *provisionally* rejected claims 1-11, 13-19, 27-37, and 39-45 for alleged nonstatutory obviousness-type double patenting over claims 1-13 of co-pending U.S. Application No. 10/535,231. The Examiner recognizes that these claims are not identical, but asserts that they are directed to nearly the same polypeptide conjugates and compositions.

Applicants traverse this rejection. Nonetheless, since this is a *provisional* rejection, Applicants will address this issue upon the indication of allowable subject matter in this or the other application.

Applicants believe that all of the claims in the application are presently allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

/William T. Christiansen/
William T. Christiansen, Ph.D.
Registration No. 44,614

WTC:jto

701 Fifth Avenue, Suite 5400
Seattle, Washington 98104
Phone: (206) 622-4900
Fax: (206) 682-6031

1304498_1.DOC